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Abstracts for the Ninth Annual Scientific Conference of the Prader-Willi Syndrome (PWS) Association

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INTRODUCTION

The Ninth Annual Scientific Conference of the Prader-Willi Syndrome (PWS) Association (USA) met in Atlanta on July 20, 1994. The 17 papers which were presented ranged from those which explored the molecular origins of PWS to those that studied the most effective medical, behavioral, and nutritional management of affected children and adults.

Several important messages emerged. The first was that although most patients with PWS have an interstitial deletion of 15q11q13 of paternal origin, and a smaller percentage of patients have maternal disomy, there can be several other morphologic alterations of chromosome 15 which cause PWS. As our understanding of these changes at the molecular level improves, we will better understand the nature of these unusual rearrangements.

Several clinically important points were also made. An important warning for the unsuspecting clinician, was the observation by Rogan et al. (Abstract 6) that uniparental maternal disomy in PWS significantly increases the risk for the expression of rare, recessive genes on chromosome 15 due to isodisomy. Finally, an important theme, echoed in several papers, was the avoidance of obesity to prevent major causes of morbidity and mortality.

The format of this meeting was refreshing, since it gave the researcher interested in a specific disorder two important opportunities. The first was to share and learn from other investigators who worked on the same disorder, but outside of their own discipline. The second, and perhaps more important, was that by having the scientific session coincide with the national meeting for PWS families, researchers met affected individuals and relatives, discussed their own work, and listened to the concerns of the families. This interaction with patients and families often reignites an investigator's dedication. It is a format which worked well and should be considered by other organizations.

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ABSTRACT 1: CYTOGENETIC AND MOLECULAR GENETIC CHARACTERIZATION OF 57 INDIVIDUALS WITH PRADER-WILLI SYNDROME

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Prader-Willi syndrome (PWS) is characterized by hypotonia, early childhood obesity, mental deficiency, hypogonadism, and an interstitial deletion of 15q11q13 of paternal origin in 50–70% of patients. The remaining patients have submicroscopic deletions, maternal disomy, or other anomalies of chromosome 15.

We have undertaken cytogenetic and molecular genetic studies of 57 individuals (28 males and 29 females; age range, 3 months–38 years), 25 with recognizable 15q11q13 deletions (44%), 28 with normal-appearing chromosomes (49%), and 4 with other chromosome 15 anomalies (7%). These patients presented with features consistent with Prader-Willi syndrome. High-resolution chromosome analysis and single or multiple polymerase chain reaction (PCR) amplification, utilizing 17 STRs from the 15q11q13 region (D15S541, D15S543, D15S11, D15S63, SNRPN, D15S128, MN1, D15S10, D15S210, D15S122, D15S113, GABRB3, D15S97, GABRA5, D15S156, D15S219, and D15S165) were performed on all patients. Quantitative Southern hybridization, using seven 15q11q13 probes (34, 3-21, 4-3R, IR10, 189-1, IR39, and small nuclear ribonucleoprotein (SNRPN)), was also undertaken on 47 patients. Fluorescence in situ hybridization (FISH), using four 15q11q13 probes (4-3R, SNRPN, 3-21, and GABRB3) was done on 18 patients. The 15q11q13 deletion was confirmed using molecular genetic techniques on 24 of the 25 PWS deletion patients. The deletion was paternal in origin in all PWS families studied genetically to date (i.e., 16 of 16 families). The size of the deletion was variable in that 5 of the deletion patients showed a nondeletion status (e.g., copy number of 2) for the proximal probe, IR39, while 5 different deletion patients showed a nondeletion status for the distal probe, IR10. Parental DNA studies from 20 of the 28 nondeletion patients showed maternal disomy in 7 patients, and biparental inheritance in 13 nondeletion patients.

In order to evaluate for submicroscopic deletions, PCR amplification with several loci (e.g., D15S128, MN1, D15S63, D15S122, or D15S10) in the area of the PWS minimal critical region, FISH using SNRPN (from

Oncor, Inc., Gaithersburg, MD), and quantitative Southern hybridization using a PCR product generated from primers of exons E and H of the SNRPN gene were undertaken on the nondeletion patients. Quantitative Southern hybridization using SNRPN was performed on 15 nondeletion patients (7 with biparental inheritance on chromosome 15, 4 with maternal disomy; parental DNA was not available on 4 patients), and 3 of the 15 patients showed a copy number of 1 or a deletion status. FISH with SNRPN confirmed these findings. Thus, 3 of the 11 nondeletion patients (excluding known cases of maternal disomy) showed a submicroscopic deletion of 15q11q13 using probe PW71B. Our study further supports the need to apply both cytogenetic and molecular genetic methods for characterizing the genetic status of PWS patients.

ABSTRACT 2: A BOY WITH PRADER-WILLI SYNDROME DUE TO FAMILIAL TRANSMISSION OF DUPLICATION OF CHROMOSOME 15 (Q11–13)

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It is well-documented that Prader-Willi syndrome (PWS) can be caused by either paternal deletion or a maternal disomy at the 15q11–q13 region. There have also been several instances of duplications of this same region in individuals with or without PWS. We report on a patient with PWS phenotype associated with duplication of 15q11–q13 present in three generations.

The propositus was a 7-year-old boy referred for evaluation of PWS; typical manifestations of PWS were noted. High-resolution G-banding chromosome analysis revealed one chromosome 15 to have a small duplication in the proximal long arm [dup(15)(q11.2→q13)]. The same duplication was also found in the phenotypically normal mother and maternal grandfather. Fluorescence in situ hybridization (FISH) with the DNA probe p5151, specific for the Prader-Willi/Angelman region of chromosome 15q, confirmed the duplication in proximal 15q. Further evaluation of the duplication of chromosome 15 (q11–q13) using dinucleotide repeat polymorphism markers is in progress.

Our data confirm the association of duplication 15q11–q13 with PWS, and we suggest that further investigation of duplication cases by FISH and other molecular techniques is warranted.

ABSTRACT 3: A FORM OF DUPLICATION MAY BE A NORMAL EUCHROMATIC VARIANT

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It is widely recognized that deletion involving 15q11.2–q13 leads either to Prader-Willi or Angelman syndrome, depending on whether the deletion is paternal or maternal. It has also been reported that duplication or triplication of 15q11.2–q13 may lead to phenotypic anomalies often including Prader-Willi or Angelman syndrome-like features. In one study, 16/27 bisatellited accessory (chromosome 15) with two copies of PWS/AS robe hybridizations had a significant association with an abnormal phenotype [Leana-Cox et al., Am J Hum Genet 54:748–756, 1994]. By contrast, a number of cases have also been reported in which duplication of 15q11.2–q13 have not been associated with any detectable phenotypic abnormality. Ludowese et al. [Clin Genet 40:194–201, 1991] have summarized 25 such cases from several unrelated families.

In the last 3 years, we have observed "duplications" similar to those reported by Ludowese et al. [Clin Genet 40:194–201, 1991] in 18 individuals from 8 unrelated families. In 1 patient, prenatal chromosome analysis demonstrated a karyotype of 46,XY,?dup(15)(q11.2–q13). The mother's chromosomes were normal, but the phenotypically normal father had the same unusual chromosome 15. The dup(15)(q11.2–q13) chromosome had a single normal pattern for the PWS/AS probes A and B, and SNRPN hybridization in the father and the fetus. We have observed normal FISH patterns by these probes in several other families with similar variant 15 chromosomes. To determine whether the duplication was of chromosome 15 origin, we analyzed G banded metaphases sequentially by a chromosome 15 paint probe in the father. The duplicated segment paints with CSP-15. Using PCR amplification, we analyzed the father's DNA at 5 loci for highly polymorphic dinucleotide repeats mapped to the 15q proximal region near the centromere. One of these loci was uninformative, and the other four were heterozygous, and the two alleles were of equal intensity, suggesting no duplication.

The critical region probes A (IR4-3R), B (GABRB3), and SNRPN are known to be at the boundary of 15q11.2–q12 [Mutirangura et al., Hum Mol Genet 2:143–151, 1992]. We suggest that amplification or duplication of distal 15q12 and 15q13 results in a normal euchromatic variant. These cases seem to have unduplicated copies of 15q11.2, including the PWS/AS critical region at the boundary of 15q11.2–q12 [Jalal et al., Am J Med Genet, 52:495–497].

ABSTRACT 4: PATERNAL TRIPLICATION OF 15Q11–Q13 IN A HYPOTONIC, DEVELOPMENTALLY DELAYED CHILD WITHOUT PRADER-WILLI OR ANGELMAN SYNDROME

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Genetic imprinting of the maternally-derived Prader-Willi chromosome region (PWCR) between 15q11–q13 is responsible for the phenotype observed in Prader-Willi syndrome (PWS). Inactivation, presumably by methylation of maternal genes in this region, is normal; absence of the normally active paternal genes, by paternal deletion or maternal uniparental disomy, causes PWS. Two cases of triplication of the maternal 15q11–q13 region have been previously reported by abstract. We have seen a patient in whom detailed molec-

ular analysis demonstrated triplication of the paternal 15q11–q13 region.

S.S., a female, had a history of decreased fetal movement beginning 1 month prior to estimated date of confinement (EDC). Delivery was by emergency cesarean section for face presentation. Birth weight and length were at the 10th centile, but she had neonatal hypotonia with poor cry, and suck requiring large holed nipples. She has developmental delay, walking at age 2 years, speaking words at 2.5 years, and sentences at 6 years. She was mildly obese as an infant, but 50th centile for weight and 5th centile for height at 6 years. Head is 75th centile. She has violent and repetitive behavior, and a high pain tolerance. She has a wide mouth, but is otherwise physically and neurologically normal and in good health.

Using high-resolution cytogenetics and fluorescence in situ hybridization (FISH) for D15S11 and GABRB3, we found three tandem copies of 15q11–q13 on the abnormal chromosome, and one on the normal chromosome 15. D15S17, which is outside the PWCR, was present in only one copy on both chromosomes. Methylation studies with PDN34 suggest that the three copies are paternally inherited. PCR studies with GABRB3, D15S11, and D15S113 indicate that both alleles from the father are present in the triplicated region.

The 2 patients reported by abstract with maternal triplication of q11–q13 were 7 months and 28 months old and were also hypotonic and developmentally delayed. In addition, they had visual disturbance. The older one had growth at the 10th centile, the younger at the 50th centile. No consistent pattern of minor anomalies were noted.

Since only the paternal PWCR and the maternal Angelman syndrome (AS) chromosome region are normally active, our patient would be expected to show effects only of the excess paternal PW alleles. However, her findings were nonspecific, as were those of the previously reported patients with excess maternal alleles (who should have had extra copies of the active AS alleles). It may be that the imprinting process prevents expression of excess alleles in this region by a process other than methylation.

The use of FISH, PCR, and methylation analysis of 15q11–q13 in such unusual cases can aid understanding of the effects of imprinting in this region and the search for candidate genes for PWS and AS.

ABSTRACT 5: UNUSUAL CHROMOSOMAL REARRANGEMENTS IN TWO PATIENTS WITH FEATURES OF PRADER-WILLI SYNDROME

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Two patients are described who demonstrate unusual chromosomal rearrangements and manifestations of Prader-Willi syndrome (PWS). A.M., who shows many of the classic manifestations of Prader-Willi syndrome, has maternal uniparental disomy for chromosome 15, having inherited a balanced Robertsonian (13;15) translocation from his mother, along with his mother's normal chromosome 15. This seems to have involved a nondysjunction during meiosis I, since A.M. shows maternal heterodisomy for markers close to the centromere, and maternal isodisomy for a marker located near the 15q terminal. This is the third reported case of PWS associated with a balanced Robertsonian (13;15) translocation.

R.H. has maternal uniparental isodisomy for the entire chromosome 15, due to a de novo isochromosome 15. He poses an interesting diagnostic dilemma, having demonstrated many features of PWS when he was younger, and many features of Angelman syndrome (AS) as an adult. He demonstrated decreased intrauterine activity, neonatal hypotonia, feeding difficulties, cryptorchidism, underdevelopment of the scrotum, and childhood obesity with a waddling gait. However, at age 37 years, his height and weight are both <10th centile. He has facial features characteristic of AS, a Stanford-Binet IQ of 3, says very few words, and exhibits constant laughing and hand clapping. Maternal uniparental disomy has invariably been associated with PWS. Further work is in progress in an attempt to determine the molecular mechanism responsible for R.H.'s phenotype, especially the apparent contradiction inherent in having maternal uniparental disomy and AS characteristics.

ABSTRACT 6: COINHERITANCE OF OTHER CHROMOSOME 15 ABNORMALITIES WITH PRADER-WILLI SYNDROME: GENETIC RISK ESTIMATION AND MAPPING

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Congenital abnormalities involving genes on chromosome 15 other than those responsible for Prader-Willi syndrome (PWS) may account for unusual variant phenotypes seen in PWS patients. Maternal recessive alleles at disease loci that are not intrinsic to the PWS phenotype but which are linked to the PWS locus can be unmasked in patients with paternal deletions of 15q11–q13 [Lee et al., N Engl J Med 330:529–534, 1994]. In contrast, uniparental maternal isodisomy can result in the reduction to homozygosity of heterozygous, recessive maternal genes that may be located anywhere on the long arm of chromosome 15 [Woodage et al., Am J Hum Genet, 55:74–80, 1994]. We demonstrate that uniparental disomy (UPD) in PWS *substantially* increases the risk of the expression of rare, recessive genes due to isodisomy. The likelihood of inheriting

a dominant condition should be similar in both PWS and in individuals exhibiting Mendelian inheritance; however, the proportion of PWS patients with a severe (or lethal) form of this disease will be increased relative to the general population, again because of isodisomy at this genetic locus. For loci proximal or distal to the canonical PWS deletion breakpoints, this risk is the product of the population allele frequency and the probability of isodisomy at the disease locus. These probabilities have been determined from a data base consisting of the genotypes of 28 genetic loci that span chromosome 15 for 90 PWS patients with UPD. For recessive loci that map within the deletion interval, this risk is increased by the probability of inheriting one of two maternal chromosomes carrying the mutant allele. We have estimated the relative risks of jointly inheriting PWS and Tay-Sachs disease, Bloom syndrome, Marfan syndrome, limb girdle muscular dystrophy, oculocutaneous albinism (type II, tyrosinase-positive), or autism, assuming that a single gene on chromosome 15 is responsible for each of these conditions. Other rare recessive conditions that were previously assumed to arise sporadically may be recurrent in the PWS population with UPD. The cause of these disorders may not be known. We present an approach to localize such genetic loci, based on linkage analysis of artificial, inbred pedigrees, in which PWS probands inherit chromosome pairs that are identical-by-descent. Simulation studies indicate that <10 PWS individuals with UPD affected with recessive, single-gene disorders are required to detect significant linkage to a nearby polymorphic genetic marker.

ABSTRACT 7: AN APPARENT RECOMBINANT CHROMOSOME 15 WITH CRYPTIC ISODISOMY AND PRADER-WILLI SYNDROME

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Prader-Willi syndrome (PWS) is a clinically recognizable disorder manifesting with hypotonia in the neonatal period, failure to thrive in infancy and early childhood, rapid weight gain after age 1 year, characteristic facial manifestations, hypogonadism, mental retardation, and hyperphagia. In most cases, PWS results from a chromosome deletion of 15q11.2–13. The remaining patients have normal-appearing chromosomes, some of which represent cases of uniparental disomy (UPD) for chromosome 15.

We report on an 11-year-old girl who upon clinical examination fulfilled the major and most of the minor diagnostic criteria for PWS. She is presently 41.8 kg, and 131.7 cm in height. She has the typical PWS phenotype. Notable are her dark brown hair and brown eyes.

The result of an initial high-resolution chromosome study of this patient was normal, 46,XX. Further investigation of chromosome 15 origins in this patient, using Q-banding techniques, showed a chromosome 15 heteromorphism of one homolog not found in either parent. Both chromosome heteromorphism and DNA variable number tandem repeats (VNTRs) analysis (TBQ7, D10S28; EFD52, D17S26; YNH24, D1S44; CMM101, D14S13), however, indicated >99.99% probability of paternity and maternity. Polymerase chain reaction (PCR) was subsequently performed using three primer sets (D15S11, GABRB3, and GABRA5) specific for microsatellite repeats in the PWS critical region 15q11.2–13. Results indicated that the index case had not received any paternal contribution and in fact was isodisomic for this region. Fluorescence in situ hybridization (FISH) of patient and parent chromosomes with probes D15S11, SNRPN, D15S10, and GABRB3 (Oncor, Gaithersburg, MD) showed normal hybridization signals for each of these four probes. To better characterize the rearranged derivative chromosome 15 homolog, quinacrine and distamycin/4′-6-diamidino-2 phenylindole (DAPI) special staining were performed. The resulting banding patterns showed that a de novo translocation had occurred, giving the derivative 15 an altered satellite region. DAPI staining, which is specific in the acrocentric group to the chromosome 15 short arm, gave an unusual DAPI pattern in both the mother and index case, in that they both had a chromosome 14 homolog with a DAPI-positive region on the short arm. This DAPI-positive chromosome 14 is maternally inherited in the index case, but had a different chromosome 14 short arm than that of the mother. From these data, we postulate that translocation, recombination, and/or abnormal segregation events occurred, contributing to the resulting uniparental disomy.

ABSTRACT 8: MOLECULAR CYTOGENETIC ANALYSIS OF A PRADER-WILLI SYNDROME PATIENT WITH A DE NOVO 46,XY, t(15;19)(q12;q13.41)

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A 3½-year-old boy with Prader-Willi syndrome was recently found to have a de novo 46,XY, t(15;19)(q12; q13.41) karyotype. Fluorescence in situ hybridization (FISH) studies were performed with probes D15S11, SNRPN, D15S10, and GABRB3 (Oncor, Inc., Gaithersburg, MD). The chromosome breakage occurred inside the SNRPN cosmid contig. To further characterize the breakpoint, we designed PCR primers to amplify the coding region of the SNRPN gene. An RT-PCR product (1,020 bp) from total human brain mRNA, covering SNRPN exons 1–8, was used as a probe with genomic DNA and Southern hybridization. An extra DNA band about 20 kilobases (kb) in size was detected from our patient's genomic DNA, using addition, PCR studies of DNA loci D15S541, D15S543, D15S63, D15S128, D15S10, and GABRA5 showed heterozygosity, while MN1, D15S122, and D15S65 showed only one allele each, indicating either a deletion or more likely homozygosity for these three loci. D15S128 and GABRA5 showed biparental inheritance, ruling out uniparental disomy.

Our results indicate that the breakage occurred upstream to exon 1 of the SNRPN gene within a 6-kb re-

gion. Our research raises four possibilities to account for the Prader-Willi phenotype of this patient: 1) the translocation disrupted the regulatory sequences of the SNRPN gene; 2) there might be additional exons of the SNRPN gene upstream to exon 1, and the breakpoint is between exon 1 and the upstream exon; 3) the translocation positioned a transcriptional repressor in the vicinities of the SNRPN gene or of another gene near the SNRPN gene; or 4) the translocation disrupted another gene upstream to SNRPN, possibly the proposed imprinting control element (ICE).

ABSTRACT 9: GROWTH VELOCITY, WEIGHT, AND BODY COMPOSITION CHANGES AFTER GROWTH HORMONE THERAPY IN PRADER-WILLI SYNDROME

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Obesity and short stature are common manifestations of Prader-Willi syndrome (PWS). We have previously reported on neurosecretory growth hormone (GH) dysfunction and the benefits of GH therapy in 15 children with PWS. After evaluating 48 PWS patients, including 4 adults, we found decreased spontaneous 24-hr GH secretion in all but one 18-month-old child with maternal disomy. Eleven of these patients were considered nonobese, based on their body mass index (BMI) [BMI = Wt(kg)/Ht $(m)^2$] for their age. GH-binding protein measured in 12 patients showed low–normal levels in all but one. Twenty-four children have completed at least 1 year of GH therapy (0.2–0.3 mg/kg/week). Growth velocity increased from 4.7 ± 1.7 cm to 10.03 ± 2.4 cm in 16 males, and from 4.25 ± 1.6 cm to 8.9 ± 2.1 cm in 8 females. Weight standard deviation for age decreased significantly from 3.4 ± 1.9 to 2.0 ± 1.4. Body composition measured in 12 children demonstrated significant decrease in fat mass from 40 ± 6% to 27 ± 6%, and increase in lean mass from 60 ± 6% to 73 ± 6% after 9 months of therapy (Fig. 1).

BMI decreases significantly after GH therapy in PWS children, but it may reach its plateau before acceptable values. BMI, however, is not an actual measurement of body fat, and therefore, body composition could be an additional and significant parameter to evaluate the lipolytic effect of GH in PWS individuals with or without weight loss.

ABSTRACT 10: SALIVARY ABNORMALITIES IN PRADER-WILLI SYNDROME

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Abnormal saliva is a well-documented finding in individuals with Prader-Willi syndrome (PWS). It has been suggested that abnormal saliva may be a diagnostic indicator of PWS in neonates [Stephenson, AJDC 146:151–152, 1992]. Despite its inclusion as one of the minor criteria for assigning a diagnosis of PWS, little is known about saliva in these individuals.

Previous studies of 4 patients with PWS demonstrated that whole salivary flow rates (both stimulated and unstimulated) were <20% of that for controls [Bray et al., Medicine (Baltimore) 62:59–80, 1982]. We have recently undertaken a study to characterize the composition of saliva from PWS patients, to see if there is any correlation with the underlying molecular diagnosis (deletion vs. disomy). We have collected whole saliva from 3 patients. Two of these patients had normal high-resolution chromosome analysis (patients 1 and 2). Patient 1 also had normal FISH analysis with a cosmid probe derived from IR4-3R. Neither patients 1 nor 2 has had subsequent molecular analysis. Patient 3 has a deletion of 15q11q13. Our results are shown in Table I.

The flow rates of patients 1–3 are similar and consistent with those reported by Bray et al. [1982]. The concentrations for all three PWS individuals are similar and are significantly different from normal controls ($P < 0.05$). For all parameters, patient 3's values were notably different from those of his unaffected sib. Although these data are from only 3 PWS individuals, it provides us with valuable information. First, decreased flow appears to be due to an effect of PWS and not of medications, since patients 2 and 3 were not taking any medications. Second, decreased flow appears to be present in

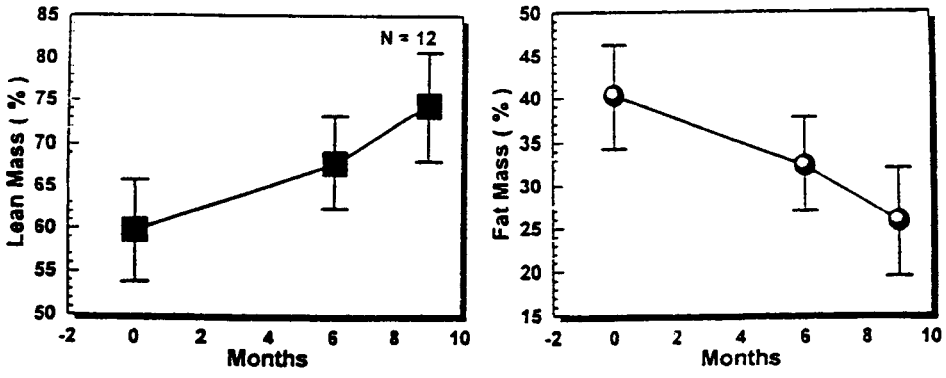

Fig. 1. Changes in body composition of 12 children with PWS after 9 months of therapy with growth hormone.

TABLE I. Flow Rates and Mineral Concentrations of Saliva From PWS Patients and Controls

Subject	Age (years)	Flow rate (g/min)		Concentration (unstimulated saliva)			
		Unstimulated	Stimulated	Fluoride (μM)	Calcium (mM)	Phosphorus (mM)	Protein (mg/ml)
Case 1	53	0.20	0.45	6.95	2.66	7.89	1.4
Case 2	21	0.18	0.42	6.37	2.89	9.20	1.8
Case 3	8	0.18	0.37	6.16	3.66	13.59	2.0
Case 3's sib	12	0.85	2.70	4.42	1.37	4.46	0.55
Xerostomic Subjects		—	0.20 (0.07)	14.2 (4.9)	1.32 (0.18)	2.95 (0.37)	
Controls		0.54 (0.12)	2.38 (0.57)	3.74 (0.70)	1.19 (0.05)	4.00 (0.14)	0.70 (0.09)

younger as well as older individuals. Third, deviations from normal in the salivary composition are evident. It is possible that these alterations are concentration effects relative to a decrease in flow rate. We are currently obtaining saliva from more PWS individuals to see if these alterations are present in all PWS individuals, and whether they can be applied as a screening test.

ABSTRACT 11: IDENTIFICATION OF FOOD ATTRIBUTES THAT INFLUENCE CHOICE OF FOODS AND FOOD PREFERENCES IN INDIVIDUALS WITH PRADER-WILLI SYNDROME

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The senses of taste and smell play a crucial role in our acceptance and rejection of food. Innate preferences for sweet tastes help us identify nutritious foods, and innate aversion to bitter taste helps us avoid foods that may be harmful. In this study we compared the senses of taste and smell and food preferences of individuals with Prader-Willi syndrome (PWS) with their nonaffected sibs. The results of this preliminary investigation do not show any differences in the functions of taste and smell between the two groups. Furthermore, PWS individuals seem to show very similar patterns of food preferences to their nonaffected sibs: familiar foods are preferred to unfamiliar ones, and sweet and salty foods are preferred to sour and bitter foods. However, many more attributes remain to be examined, and more extensive study of the chemical senses is necessary before any meaningful conclusions may be drawn. A better understanding of the sensory and cognitive attributes of food that influence the eating patterns of PWS individuals may help clarify the mechanisms underlying the aberrant eating behavior associated with the syndrome.

ABSTRACT 12: ACUTE GASTRIC DILATION AND GASTRIC NECROSIS AND DEATH IN INDIVIDUALS WITH PRADER-WILLI SYNDROME

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Hyperphagia is the predominant clinical manifestation in individuals with Prader-Willi syndrome (PWS). When uncontrolled, it leads to morbid obesity, the principal cause of morbidity and premature mortality in this syndrome. Further, this appetite disorder is thought to be central in origin. Although studies have reported abnormal gut neuropeptide responses to protein meal challenges, peripheral manifestations of gastrointestinal disorder are absent in the PWS literature.

We report on 2 individuals with PWS with unexplained gastric dilatation leading to subsequent gastric necrosis. Both individuals were females in their early twenties. Neither was significantly obese at presentation. Both women presented to emergency rooms with vague abdominal pain which had progressed to vomiting. Clinical examination was significant for mild abdominal distention only. Initial diagnoses were viral gastroenteritis. In both, symptoms and signs progressed insidiously over the next 12–24 hr to severe abdominal pain and vomiting with subsequent gastric rupture, peritonitis, and shock. One patient succumbed to overwhelming sepsis. The other recovered after a prolonged hospitalization.

Pathological examinations of the stomachs showed diffuse mucosal infarction with multifocal transmural necrosis. Vascular dilatation and small fibrin thrombi were apparent within the infarcted areas. Ghostly outlines of mucosal glands were visible in many areas with only mild inflammatory changes suggesting the process was acute, i.e., 24–48 hr in duration. No vasculitis, major vessel thrombosis, embolus, or vascular malformation were seen. There was no evidence of volvulus or mechanical vascular obstruction at surgery.

These 2 young women presented with benign clinical symptoms which progressed to gastric necrosis. Total gastric necrosis is a rare but catastrophic event. Cause includes intrathoracic gastric herniation, volvulus of the stomach, acute necrotizing gastritis, ingestion of caustic material, and acute gastric dilatation usually secondary to psychogenic polyphagia. The presentations here with vague abdominal pain, vomiting, and distention may be most consistent with acute necrotizing gastritis. There is no clear cause to this disorder. The recent finding of a gene for the small nuclear ribonuclearprotein polypeptide N (SNRPN) has been found that maps to the critical region on chromosome 15. SmN, a core protein of SNRPN, acting in regulating tissue-specific splicing, may function as a *trans*-acting factor promoting calcitonin gene-related peptide (CGRP) mRNA production. CGRP is also believed to regulate gastrointestinal homeostasis. Therefore, one may spec-

ulate that abnormalities in CGRP expression in individuals with PWS may predispose these patients to unusual gastric injury.

ABSTRACT 13: AGE AND CAUSES OF DEATH IN PRADER-WILLI SYNDROME PATIENTS

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The experiences of seven physicians from five states and Canada who care for approximately 665 Prader-Willi syndrome (PWS) patients were accumulated to ascertain causes of death and age at death. Twenty-five deaths occurred in patients between ages 1–38 years; average age at time of death was 20 years. Fifty-six percent (14 patients) of deaths were due to obesity, at an average age of 23 years. The remaining 11 patients died of 10 other causes. Nineteen patients (76%) died as a direct result of PWS. An additional three deaths (12%) were unrelated to PWS. The oldest patient presently cared for by this group of physicians is 62 years old. Approximately 14% of these 665 patients are over 30 years of age. We conclude that the most common cause of death in PWS is obesity; however, one fourth of the deaths were not directly related to the syndrome. It is also apparent that many patients live well beyond age 30 years.

ABSTRACT 14: THE HISTORY, CURRENT USE, AND IMPACT OF PSYCHOTROPIC MEDICATIONS FOR MANAGING MOOD AND BEHAVIOR VOLATILITY IN PERSONS WITH PRADER-WILLI SYNDROME

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This report summarizes a three-part study investigating the history, current use, and impact of mood-altering and behavior-change medications as a method of behavior management in adolescents and adults with Prader-Willi syndrome (PWS).

In phase 1, the history of and current use of psychotropic medication was surveyed for 114 persons with PWS living either at home or in one of three out-of-home settings: 1) dedicated residential programs containing only persons with PWS, 2) integrated group homes with both PWS and other MR adults, and 3) supervised apartment living. Phase 2 expanded the data base to include 78 currently medicated cases randomly drawn from an acute (crisis) care treatment program and from a questionnaire about the use of Prozac, that was developed by the PWS Association. Phase 3 employed a modified case-control methodology utilizing medical records to determine behavioral changes in response to psychotropic medications.

Two striking findings include: 1) most medications are administered for behavior symptoms of tantrum, argumentativeness, and stubbornness rather than for any specific diagnosis; and 2) extraordinarily few medications had any effect and among those that did, most were so toxic that they rendered the patients nonfunctional. Serotonin reuptake inhibitors consistently emerged as the most useful, however, with differential impact on cognitive functioning. Many individuals demonstrated an idiosyncratic response to these medications. Initial response was often immediate and dramatically positive, with a subsequent reemergence of suppressed behaviors after 2–3 weeks. Subsequent protocols indicated that while the initial dose was appropriate, over time it reached toxic levels, causing increased agitation and irritability. In most cases, reducing the dose was effective.

Future studies are needed to determine the impact of long-term use.

ABSTRACT 15: CORRELATES OF MALADAPTIVE BEHAVIOR IN CHILDREN AND ADULTS WITH PRADER-WILLI SYNDROME

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Four correlates of maladaptive behavior were examined in 25 children and 61 adults with Prader-Willi syndrome (PWS): age, gender, IQ, and body mass index (BMI). Maladaptive behavior was assessed in children with the Reiss Scales for Children's Dual Diagnosis, and in adults with the Reiss Screen for Maladaptive Behavior. As the Reiss Scales and Screen do not have comparable domains, separate multivariant analyses of variance (MANOVAs) were conducted in age group.

Age emerged as a significant correlate in children, with older children showing increased symptomatology relative to younger subjects, especially in depression and withdrawal. Among adults, changes in maladaptive behavior appeared nonlinear, with both steady and variable behavioral expressions. Boys showed more severe depression relative to girls; those findings were not seen in the adults. No maladaptive behavior differences were found in high vs. low IQ subjects. Intriguingly, thinner adults with lower BMIs had higher maladaptive behavior scores relative to heavier subjects, particularly in internal states involving distressful affect and problems with thinking (see Table II). We offer three explanations of these counterintuitive BMI findings: a reporting bias; stress in thinner subjects; and misconceptions of PWS.

ABSTRACT 16: EDUCATIONAL SETTINGS AND PARENT SATISFACTION IN A TIME OF CHANGING EDUCATIONAL SERVICE DELIVERY MODELS: A SURVEY OF PARENTS OF CHILDREN WITH PRADER-WILLI SYNDROME IN THE NEW ENGLAND REGION

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The recent national movement towards "inclusion" is resulting in increasing numbers of children with Prader-Willi syndrome (PWS) being educated in regular classroom settings alongside typically developing children. The implementation of new and varied service delivery models creates substantial need for the study of factors necessary for the provision of successful educational programming for children with PWS. One index of successful educational programming is parents' satisfaction with their child's program.

Currently in New England, an area which is in transition in terms of educational models for children with special needs, children with PWS are enrolled in a diverse range of educational settings, from regular classrooms, with an array of supports, to residential schools. This study was conducted to explore factors impacting families' satisfaction with their children's educational placement and experience.

Families in the New England region with a child or adolescent with PWS between age 3–22 years (N = 30) responded to a telephone survey. To delineate current practices in placements, associations between child factors (e.g., age of child, parental perception of child's degree of intellectual and behavioral challenge) and educational setting prototype was explored through chi-square analyses. Factors associated with parent satisfaction with their child's educational experience, including classroom prototype and types of supports, were also explored through chi-square analyses.

Results were discussed in terms of current trends in placement, and in considerations for maximizing parent satisfaction with the educational settings for their children with PWS.

TABLE II. Means and *F* Values of Reiss Domains in Thinner vs. Heavier Prader-Willi Subjects

Domain	Thinner (low BMI)	Heavier (high BMI)	*F*
Psychosis	2.98	1.58	4.76*
Confused thinking	.71	.31	5.83**
Delusions	.54	.17	4.48*
Hallucinations	.27	.00	5.46*
Paranoia	.64	.55	.21
Social inadequacies	.82	.55	1.95
Depression behavioral	3.36	1.88	5.82*
Anxious	.75	.36	5.38*
Crying spells	.64	.46	1.24
Fearful	.36	.10	4.24*
Overly sensitive	.86	.57	2.04
Sadness	.75	.39	3.72*
Dependent personality	3.87	2.07	4.72*
Anxious	.70	.34	4.82*
Attention-seeking	.89	.52	3.48
Body stress	.70	.38	3.25
Complaining	.79	.45	2.75
Dependent	.79	.38	4.36*

* $P < .05$.
** $P < .05$.

ABSTRACT 17: MULTIDISCIPLINARY APPROACH TO THE PATIENT WITH PRADER-WILLI SYNDROME

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Prader-Willi syndrome (PWS) is a complex disorder involving somatic and psychological abnormalities. Since the pathogenesis and possible interplay of the syndrome components have not been completely defined, current treatment of a child with PWS ideally involves coordinated attention to the various syndrome manifestations. However, with few exceptions, clinical management is often fragmented among two or more specialty clinics, often leading to confused treatment planning. As an outgrowth of our multidisciplinary research studies defining the clinical characteristics of PWS, we have designed a coordinated "one-stop" outpatient for children with PWS. This report describes the design and function of the Texas Children's Hospital Prader-Willi Syndrome Clinic. Clinic staffing includes physician specialists in gastroenterology, genetics, endocrinology, and psychiatry, a nutritionist specializing in eating disorders, a gastroenterology research nurse, and an exercise physiologist. Affiliated services include specialists in adolescent medicine and neurophysiology, body composition laboratory, sleep laboratory, and exercise physiology laboratory. Upon referral, patients are first evaluated by the geneticist. Upon genotypic and phenotypic confirmation of the diagnosis, nutritional evaluation and counseling are immediately initiated with a goal toward behavioral control of food intake and maintenance of acceptable weight-gain patterns. An exercise program is also recommended, based on age and capabilities. After age 5 years, and after assurance of adequate weight control, patients are evaluated by an endocrinologist and consideration is given for growth hormone therapy. The timing of these evaluations is based, in part, on our research experience, and evaluations are individualized according to the needs of each patient. Psychiatric evaluation/counseling and body composition analysis are performed at each clinic visit; muscle strength/exercise testing is also performed at regular intervals. As patients reach adolescence, decisions regarding gonadal steroid replacements are reached after discussions among the various specialists, including adolescent medicine. The PWS clinic is currently running at capacity, with a current population of 36 patients, 14 of whom are receiving growth hormone treatment. This multidisciplinary approach provides a unique opportunity to simultaneously, systematically collect essential research data, and to optimize clinical treatment. Illustrative cases will be presented.